REMARKS

By the present amendment, claim 23 is amended. Thus, claims 23-37 are pending. No new matter is added as the amended claim language is fully supported by the application as filed, as explained in more detail below. The amendment cancels subject matter or places the rejected claims in better form for appeal. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

As a preliminary matter, Applicants' representatives, Joseph Meara and George Quillin thank the Examiner for courtesies extended during the combination in-person (Mr. Quillin) and telephonic (Mr. Meara) interview of December 16, 2008. During the interview the rejections of record were discussed. Tentative agreement was reached that the claims were allowable for the reasons given below, subject to the Examiner's confirmation of the amounts of acetic acid and iodobenzene diacetate described in the present application and in the cited art.

I. Claim Rejections Under 35 USC §112, First Paragraph

Claims 23 and 36 stand rejected under 35 USC §112, first paragraph, as allegedly lacking written description. "In claim 23, the amount of acetic used is listed as 1130 mol per 1 mol of 7-etyl-1,2,6,7-tetrahydrocamptothecin. This introduces new matter since according to the specification, this amount can only be 668 to 1001 mol (see page 4, line 10). Similarly, in claim 36, the amount of iodobenzene diacetate is listed as 1.9 mol. However, according to the specification, this amount can only be 0.99 to 1.85 mol (see page 4, line 13). This also introduces new matter." Office Action, page 3, line 20 to page 4, line 2. Because the working example provides support for both limitations, Applicants traverse this rejection.

Support for recitation of 1130 mol of acetic acid per mol of 7-ethyl-1,2,6,7-tetrahydro-20(S)-camptothecin in claim 23 comes from Example 1 of the present application. Example 1 describes the synthesis of 7-ethyl-1,2,6,7-tetrahydro-20(S)-camptothecin by hydrogenation in a solution of acetic acid and its subsequent oxidation in the same solution. Thus, line 12 of

Example 1 describes the amount of acetic acid used in terms of volume: "The obtained solution (80 ml) of 7-ethyl-1,2,6,7-tetrahydro-20(S)-camptothecin is immediately added under vigorous stirring into a 250 mL one-necked flask containing 22 ml (1.218 mol) of water and 0.77g (2.343 mmol) of iodobenzene diacetate." That the 80 ml refers to 80 ml of acetic acid is clear from lines 3 and 11 of the same paragraph which refer to the hydrogenation reaction being carried out in 70 ml acetic acid and which describe removal of the catalyst by filtration and subsequent washing of the catalyst cake with 10 ml acetic acid. The total volume of filtrate is thus 80 ml acetic acid. Knowing the volume of acetic acid used, one of ordinary skill in the art may readily calculate the molar amount and ratio of acetic acid to starting material used in the claimed oxidation as follows.

The molecular weight of acetic acid and its density as a liquid are well known to be, respectively, 60.05 g/mol and 1.053 g/ml (see, e.g., The Merck Index, 11th Ed. (1989), p. 49, attached for the convenience of the Examiner). Thus, the amount of acetic acid recited in Example 1 is:

$$\frac{(80\ \text{ml})(1.053\ \text{g/ml})}{(60.05\ \text{g/mol})} = 1.40\ \text{mol}$$

Since the amount of 7-ethyl-1,2,6,7-tetrahydro-20(S)-camptothecin (I) may be assumed to be approximately the same as the amount of starting 7-ethyl camptothecin (1.239 mmol = 0.001239 mol), the amount of acetic acid per mol of 7-ethyl-1,2,6,7-tetrahydro-20(S)-camptothecin is calculated as:

$$\frac{1.40\ \text{mol}}{0.001239\ \text{mol}} = 1130\ \text{mol AcOH/mol (I)}$$

Applicants submit that since the claimed reaction clearly works well at this higher amount of acetic acid, Applicants clearly possessed the claimed invention at amounts of acetic acid up to this amount.

Likewise, Example 1 describes the use of iodobenzenediacetate at a ratio of 1.9 mol per mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin. Line 14 of Example 1 describes the use of 0.77 g (2.343 mmol = 0.002343 mol) of iodobenzene diacetate. Since the amount of 7-ethyl-1,2,6,7-tetrahydro-20(S)-camptothecin (I) may be assumed to be approximately the same as the amount of starting 7-ethyl camptothecin (1.239 mmol = 0.001239 mol), the amount of iodobenzene diacetate used is:

$$\frac{(0.002343 \text{ mol})}{(0.001239 \text{ mol})} = 1.9 \text{ mol iodobenzene diacetate/mol (I)}$$

Again, Applicants submit that since the claimed reaction clearly works well at this higher amount of iodobenzene diacetate, Applicants clearly possessed the claimed invention at amounts of iodobenzene diacetate up to this amount.

Because the working example clearly provides support for the claimed methods at the recited amount of acetic acid and iodobenzene diacetate, Applicants respectfully request withdrawal of the rejection of claims 23 and 36 under 35 U.S.C. § 112, first paragraph.

II. Claim Rejections Under 35 USC §103

Claims 23-37 stand rejected under 35 USC §103(a) as allegedly being unpatentable over Lin (U.S. Patent No. 7,151,179). In the Office Action, the Examiner acknowledged Applicants' argument that the amount of acetic acid used in the claimed process differs from that used in Lin (197 mol/mol of starting material), but expressed concern that Lin did not disclose this amount. In response, during the above-noted interview Applicants' representatives explained that the working example in Lin describes the use of acetic acid, which is far different from the amount used in Applicants' claimed process.

The amount of acetic acid solvent used in Lin is set forth in the Examples at column 4, lines 7-50. The following calculations show how the molar amount of acetic acid used by Lin was derived.

First, under the title "Preparation of 7-ethyl-1,2,6,7-tetrahydro-20(S)-camptothecin (II)" Lin discloses that 30 g of 7-ethyl-20(S)-camptothecin (I) was dissolved in 900 ml of acetic acid and hydrogenated. The filtrate from this reaction was used in the following oxidation, entitled "Preparation of 7-ethyl-10-hydroxy-20(S)-camptothecin (III)." In view of this procedure, the amount of acetic acid used by Lin in the oxidation is about 900 ml. (Lin does not disclose the volume of any washings added to the filtrate).

As noted above, the molecular weight of acetic acid and its density as a liquid are well known to be, respectively, 60.05 g/mol and 1.053 g/ml (see, e.g., The Merck Index, 11th Ed. (1989), p. 49). The amount of acetic acid used by Lin is therefore

$$\frac{(900\ \text{ml})(1.053\ \text{g/ml})}{(60.05\ \text{g/mol})} = 15.78\ \text{mol}$$

The amount of 7-ethyl-1,2,6,7-tetrahydro-20(S)-camptothecin (II) used by Lin in the oxidation is approximately the same as the starting amount of 7-ethyl-20(S)-camptothecin (I) in the hydrogenation. The latter was 30 g. Since it is known that the molecular weight of (I) is 376.41, the molar amount of (I) was (30.0 g)/(376.41 g/mol) = 0.0797 mol.

Thus the amount of acetic acid per mol of 7-ethyl-1,2,6,7-tetrahydro-20(S)-camptothecin use by Lin is

$$\frac{15.78\ \text{mol AcOH}}{0.0797\ \text{mol (III)}} = 198\ \text{mol AcOH/mol (II)}$$

This amount is slightly higher than the value (197 mol) reported in Applicants' amendment dated April 14, 2008, and the difference is attributed to rounding error in the earlier communication. The difference does not change the reasoning presented in the previous amendment that claims 23-37 are nonobvious over the cited art.

Applicants reiterate that the present methods provide surprising and unexpected results over the cited art. In particular, Applicants draw the Examiner's attention to the amount of acetic acid used in the claimed method versus the cited art. Claim 23 recites the use of 668 to 1,130 mol acetic acid per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin. This translates to a range of 38.2 ml to 64.6 ml of acetic acid per mmol of the reactant, 7-ethyl-1,2,6,7-tetrahydrocamptothecin. In contrast, the amount of acetic acid employed by the cited reference is only 198 mol per mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin, which is 11.3 ml per mmol of reactant. Hence, the claimed invention operates at a significantly more dilute solution of acetic acid than the cited reference. Even if the quantity of water used as solvent (11.3 ml/mmol) in the cited method is taken into account, the reaction still fails to reach the dilution levels found in the claimed method.

At the same time, Applicants' reaction is fast, being carried out in only 5 to 30 minutes. Further, as set forth in claim 36, the present method utilizes significantly less oxidant (0.99-1.9 mol per mol of reactant) than the cited method (2.55 mol per mol of reactant). It is also surprising and counterintuitive that the amount of oxidant could be decreased and that the reaction concentration could be decreased, but still result in a fast reaction. Finally, the higher temperature range of the claimed method (see claim 37) is also advantageous as less energy is needed for cooling and heating of the reaction mixture. There is simply no suggestion in the cited art that increasing the amount of acetic acid, and thereby decreasing reactant concentration would allow the use such a fast reaction time.

Moreover, Applicants submit that the claimed invention was made prior to the earliest priority date of the Lin reference for the reasons set forth in Applicants' previous amendment. Thus, based on the declaration of inventor Petr Dobrovolny and evidence presented therein, Lin

is not prior art to the present application under any provision of 35 USC §102 and therefore is not prior art under 35 USC §103(a). For this reason and because of the surprising unexpected results obtained with the present method, Applicants respectfully request withdrawal of this ground of rejection.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. Should any issues remain open after consideration of the present amendment and reply, the Examiner is invited to contact the undersigned so that a prompt disposition of the application may be achieved.

Respectfully submitted,

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By _____

FOLEY & LARDNER LLP
Customer Number: 23524
Telephone: (608) 258-4303
Facsimile: (608) 258-4258

Jeffrey R. Lomprey (Reg. No. 55,401)
for Joseph P. Meara
Attorney for Applicants
Registration No. 44,932